REMARKS

Claims

Claims 1-3 and 8-15 are currently under examination with claims 17-18 withdrawn from consideration due to restriction/election. Claims 19–22 are added by this paper.

Claims 4-7 and 16 are cancelled without prejudice or disclaimer.

Claim amendments

The claims are amended to use language in accordance with conventional US practice. Use claims have been converted into US process claims. Typographical and lexical errors have been corrected for.

Amended claim 1 incorporates the elements of claim 6 and 7, which are hereby cancelled. Support for the amendment of claim 1 can be further found in, for example, page 5 of the present specification and the disclosure contained in the Examples.

The amendment of claims 8, 13–15 is deemed to be self-explanatory.

New claims 19–21 are supported by, for example, the disclosure bridging pages 13 and 14 of the originally-filed specification. See also, page 10, lines 17–25 (i.e., "binding to EGFR"). Claim 22 is supported, at least, by the disclosure contained in Example 6.

It is respectfully submitted that the amendments do not recite new matter. Entry thereof is respectfully requested.

Rejoinder

In view of Applicants' amendments and upon identification of allowable subject matter, the Patent Office is courteously requested to rejoin the withdrawn method and process claims and examine them on their merits.

IDS

Copies of non-patent literature references cited in the IDS filed June 12, 2008 are enclosed herewith. Withdrawal of the objection is respectfully requested.

Priority document

A copy of the English translation of the foreign priority document DE 103 55 904.3 is enclosed herewith. The certified copy of the priority document was furnished to the USPTO on May 26, 2008. Applicants respectfully aver that the enclosed English translation of the certified copy

is accurate. See, MPEP §201.15.

USPTO Patent Application Information Retrieval (PAIR) indicates that the filing date of the International Application No. PCT/EP04/12837 is May 26, 2006. This is incorrect. The International Application was filed on December 11, 2004.

Correction thereof is earnestly solicited.

Objections

Claim 1 has been amended as per the Examiner's suggestion, rendering the objection thereof moot. The specification has been amended to establish the chain of priority and to identify the international application, although neither of this is necessary.

Withdrawal of the objection is respectfully requested.

Rejection under 35 U.S.C. §112, ¶2

Applicants thank the Examiner for her careful review of the claims. The forgoing amendments render the rejection of claims 16–18 moot.

Biological deposits

Insofar as both cetuximab (Erbitux) and matuzumab (EMD 72 000) are publically available, and the present specification provides detailed description of making/using the crystal-form antibody preparation(s) of the present invention; the Examiner's contentions with respect to enablement appear to be misplaced.

As expressly stated in §2404.02:

> A deposit is not necessary even though specific biological materials are required to practice the invention if those biological materials can be made or isolated without undue experimentation. No deposit is required, however, where the required biological materials can be obtained from publicly available material with only routine experimentation and a reliable screening test. Tabuchi v. Nubel, 559 F.2d 1183, 194 USPQ 521 (CCPA 1977); Ex Parte Hata, 6 USPQ2d 1652 (Bd. Pat. App. & Int. 1987) (Emphasis added)

With respect to the Examiner's contentions at page 7 of the Office Action, Applicants highlight the fact that US patent No. 5,558,864, which is directed to the anti-EGFR antibodies, is currently assigned to the assignee of the present application. As explicitly stated in the specification of this patent, the hybridoma cell line 425 was deposited according to Budapest Treaty at the American Type Culture Collection (ATCC) under the accession No. HB 9629. ATCC is a recognized International Depositary Authority (IDA). See, MPEP §2405. As such, the deposits

made therein satisfy the requirements under 37 CFR §1.803.

The hybridoma cell-lines which produce the antibody molecules described in US 6,217,866 (assigned to Aventis Pharmaceuticals, Inc.) have similarly been deposited in the American Type Culture Collection (ATCC catalog Nos. HB 9763 and 9764). This is explicitly taught by the specification of the '866 patent. Assuming that this deposit met the US requirements since a patent is issued, Applicant respectfully submits that the requirements under 37 CFR §1.803 are duly satisfied.

Rejections under 35 U.S.C. §112, ¶1

Applicants thank the Examiner for her careful review of the claims. The forgoing amendments render the rejection of claims 16–18 moot.

Rejections under 35 U.S.C. §102

Claims 1–3, 6–10 and 12–14 stand rejected as allegedly anticipated by Kussie et al. (WO 2006/009694; filed: June 14, 2005). Kussie was filed after the filing date of the International Application No. PCT/EP04/12837, i.e., after December 11, 2004. Hence, Kussie is not prior art.

Claim 13 is rejected under §102(e) as allegedly anticipated by Mahler's disclosure in US patent pub. No. 2004/0170632 (published: September 2, 2004). Enclosed herewith is an English translation of the German priority document (DE 10355904.3; filed: September 29, 2003). The disclosure in the priority document supports the claimed subject matter. See, for example, page 5, last paragraph, page 11, last paragraph, page 12, ¶1, paragraph bridging pages 13 and 14 and the disclosure contained in Examples 2–6 at page 47 of the priority document. It is courteously submitted that Mahler was not available until after the priority date of this application, i.e., September 29, 2003. Withdrawal of the rejections is respectfully requested.

Rejections under 35 U.S.C. §112, ¶1

Claims 1-3 and 6-18 are rejected under this section due to allegedly failing to provide adequate written description and failing to provide enablement. Applicants respectfully traverse this rejection.

Written description

The central contention with respect to the written description rejection under §112 pertains to the nature and/or description of the antibody molecules recited in the claims. It is respectfully submitted that the foregoing amendments, further in view of the Examiner's comments in the

paragraph bridging pages 13 to 14 of the present Office Action, render this rejection moot. It is further submitted that the amendments are presented purely to facilitate prosecution of the application. No agreement is to be implied.

The court in Enzo Biochem v. Gen-Probe, Inc., 323 F.3d 956, 964 (Fed. Cir. 2002) ("Enzo Biochem II") establishes a legal precedent for written description of antibody molecules. The Enzo court stated that "the written description requirement would be met for all of the claims [of the patent at issue] if the functional characteristic of [the claimed invention was] coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed." Also, the court held that one might comply with the written description requirement by depositing the biological material with a public depository such as the American Type Culture Collection ("ATCC"). Id. at 970. The court proffered an example of an invention successfully described by its functional characteristics. The court stated:

> For example, the PTO would find compliance with §112, ¶ 1, for a claim to an isolated antibody capable of binding to antigen X, notwithstanding the functional definition of the antibody, in light of the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature.

The court adopted the USPTO Guidelines as persuasive authority for the proposition that a claim directed to "any antibody which is capable of binding to antigen X" would have sufficient support in a written description that disclosed "fully characterized antigens." Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/menu/written.pdf (emphasis added). The decision in Enzo was later adopted in Noelle v. Lederman 355 F.3d 1343, 1349 (US Fed. Cir. 2004), wherein the Noelle court noted:

> Therefore, based on our past precedent, as long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen. (Emphasis added)

Applicants' claims are drawn to a genus of antibodies which bind to (i.e., anti-) epidermal growth factor receptor (EGFR) polypeptides. The functional properties (i.e., ability to interact with a well-characterized EGFR) are well-described. See, the paragraph bridging pages 5 and 6 and the patent publications cited therein. The antibody molecules claimed herein, for example, monoclonal chimeric 225 antibodies and monoclonal humanized 425 antibodies, are also well-described.

Methods for obtaining crystalline or solid forms of the antibody molecules, including methods for reconstituting such forms in stable aqueous preparations are also described. See, for example, page 7, line 28 to page 8, line 10 and the disclosure contained in the entire Examples section. Based on this information and the knowledge available to a skilled worker prior to the filing of the instant application, any antibody molecule of any length (e.g., full-length vs. fragments), form (e.g., crystal vs. solid form) and/or type (e.g., polyclonal vs. monoclonal) could be isolated and used in a manner described in Applicants' instant specification. Moreover, as long as a protein is well-characterized, such as here, a general claim to an antibody thereto has a written description. As such, it is respectfully submitted that Applicants specification satisfies the statutory requirements under §112, 1st paragraph as established under *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997)), wherein the Lilly Court held that "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." In the instant application, adequate disclosure of representative species to support a genus is clearly met by Applicants' disclosure of a number of patented humanized and chimeric antibody molecules, which are cited at page 7 of the Office Action. As for the variant molecules, these alleged lack of written description thereof is irrelevant since the recited antibodies are biologically active (when reconstituted in aqueous form) against the EGFR polypeptide. See, page 10, lines 17–25 for a description of the claim term.

As such, it is courteously submitted that these features are adequate to determine that applicant was in possession of the claimed invention. Therefore, Applicants' claims, in view of the detailed disclosure contained in the specification, are in full conformance with the written description guidelines. Withdrawal of the rejection is earnestly solicited.

Enablement

The Examiner contends that the claimed invention is non-enabled because "protein crystallization is unpredictable." He cites Weber et al. (1997) to support his arguments. Applicants respectfully traverse this rejection.

Regarding the lack of enablement rejection, Applicants courteously submit that the specification, coupled with a skilled worker's knowledge, provides adequate guidance to make and use the instantly claimed compounds. Contrary to the Examiner's contention, Applicants submit that the present disclosure provides explicit guidance on how to make and use the crystals of the present invention. Reagents and conditions that are applicable to the claimed methodology of

crystallization of the claimed molecules are described in detail. To this end, Example 2 provides a disclosure of crystallization of Erbitux with ammonium sulfate. Example 3 relates to another embodiment, wherein crystallization of Erbitux with ethanol is provided. See, pages 46–47 of the specification. Methods for visually and/or spectroscopically characterizing the crystals of the present invention (for example, with respect to size and or IR spectra) are also provided. See, Examples 6–7 at page 49 of the specification.

It is earnestly submitted that a skilled biochemist who is equipped with the claimed antibody molecules and who is familiar with the techniques and/or reagents used in crystallography would possess a definitive understanding of what is described in Applicants' claims. The claimed antibody molecules, for example, chimeric monoclonal antibody c225 or a humanized monoclonal antibody h425, were well-appreciated in the art prior to the filing date of the present application. See, page 5, ¶2 of the present specification. Furthermore, techniques for generating crystals of such antibody molecules, and use thereof, for example, in developing formulations, medicaments, and such are described in detail by Applicants' own specification. See, for example, the disclosure bridging pages 14–18 of the present specification. As such, Applicants' specification provides a fully enabling disclosure of the methods for making and using the crystals of the present invention.

With respect to fragments (for example, EGFR-binding fragments), such too were well-appreciated before the filing date of the instant application. A skilled worker can use routine techniques for generating such fragment and/or variant sequences based on parent antibody sequences. See, for example, Kohler et al., (*Journal of Immunology*, 1975). For example, the skilled worker could generate full-length anti-EGFR antibody molecules having the claimed structural (i.e., chimeric and/or humanized) and/or functional (i.e., biological activity) aspects described in Applicants' specification, and use techniques of protein chemistry (for example, pepsin or trypsin digestion) to generate fragments of such molecules that are commensurate with the claims. Such methods are conventional. See, the paragraph bridging pages 13 and 14 and the references cited therein. Alternatively, the skilled worker could rely on recombinant techniques, for example, art knowledge of cloning and/or phage display libraries to rapidly generate antibodies with slightly different structures and/or specificities compared to those derived from traditional approaches (for example, monoclonal antibodies). See, the enclosed WikiPedia reference article. Based on the structure described in Applicants' specification, any antibody, for example, a polypeptide containing all the distinct domains and/or regions of an immunoglobulin molecule or a fragment thereof, which is biologically-active, could be routinely generated. Screening techniques based on for example, dissociation constants or neutralization studies, could be additionally utilized. This constitutes

nothing more than routineness.

In view of the above remarks, it is respectfully submitted that Applicants' disclosure provides more than sufficient guidance to objectively enable one of ordinary skill in the art to make and use the claimed invention with an effort that is no more than routine within the art. The statute requires nothing more. Withdrawal of the rejection under 35 U.S.C. §112, ¶1, is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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